REMARKS

Applicants respectfully request reconsideration in view of the reasons that follow.

Claim Status:

Claims 1, 12, and 23-32 are pending, with elected claims 1, 12, 23, 25, and 32 presented for examination.

Rejections under 35 U.S.C. § 103

Claims 1, 12, 23, and 25 remain rejected under 35 U.S.C. § 103 (a) as allegedly obvious over Treon *et al.*, in view of Ohtomo *et al.*, and Chiriva-Internati *et al.*, further in view of WO 200177362, as evidenced by Porgador *et al.* Advisory Action, page 2, as well as Final Office Action, item 4, pages 2-5. Additionally, claims 1, 12, 23, 25, and 32 remain rejected under 35 U.S.C. § 103 (a) as allegedly obvious over Treon *et al.*, in view of Ohtomo *et al.*, and Chiriva-Internati *et al.*, further in view of WO 200177362, as evidenced by Porgador *et al.*, and in further view of Thurner *et al.* *Id.* at item 5, page 5. Applicants respectfully traverse the grounds for this rejection.

As Applicants explained, when a cancer antigen protein is taken into DC cells, the protein is broken into peptides of about 8-10 amino acid residues, wherein the peptides complex with a MHC Class I molecule, and the complex is presented on the surface of the DC cells. T cells are activated to the CTL, which specifically recognizes the complex and then kills cancer cells expressing the complex. Because the CTL kills only those cancer cells expressing a complex recognized by the CTL, the CTL acts in a complex-specific manner. *See* Applicants' July 2010 Response.

After considering Applicants' remarks, the PTO alleges "it was well known in the art that a full length protein is not required for inducing a T cell response, as further evidenced by Boccaccio, for example." Advisory Action, page 2.

A. Boccaccio from Advisory Action

Applicants and the PTO agree that an antigen, *i.e.*, cancer protein, is engulfed by antigen presenting cells by endocytosis and the protein is degraded into small peptides. These peptides are then presented on the cell surface nestled within a class II histocompatibility complex, and an immature T cell can either recognize or not recognize the peptides.

Applicants and the PTO deviate, however, in what triggers a T cell response. In the case of a positive recognition, the T cell matures into a cytotoxic T cell (CTC), which then will attack and kill the cancer cells. Thus, Applicants submit that the T cell response is not triggered by random parts of a protein. Furthermore, because it was unknown which part(s) of the protein would trigger such a response, it was highly probable that shortening a protein would not generate a triggering peptide.

Boccaccio *et al.* (U.S. Patent No. 7,252,996) discloses "dendritic cell culture may be completed with soluble or particulate antigens, including tumor target cell or cell debris, or specific peptides against which an immune response is expected." *See* Boccaccio, column 4, lines 35-38, emphasis added. Thus, while it is possible to present a smaller protein to dendritic cells, Boccaccio explicitly recites use of a "soluble antigen", and not any protein. An antigen is a substance that induces an immune response, thus Boccaccio's soluble antigens would inherently trigger an immune response. Furthermore, Boccaccio states that the specific peptides were only used when an immune response was expected. *Id.*, emphasis added. Because an immune response was expected, it is not surprising that Boccaccio's peptides, in fact, triggered an immune response, as the peptides appeared to have been pre-screened or otherwise pre-selected.

In contrast, the soluble form of HM1.24 protein was not expected to produce an immune response. That is, an immune response was expected only from the full length HM1.24 protein. Thus, an ordinarily skilled artisan would not have used soluble HM1.24 for pulsing an antigen-presenting cell, let alone expected the soluble form to produce an immunogenic response. Because Applicants, and not the cited art, went against convention and pulsed with soluble HM1.24, Applicants' unexpected results would not have been

predicted by any combination of the cited art. For this reason alone, the rejection is improper and should be withdrawn.

Furthermore, the present inventors surprisingly discovered that not only does pulsing with soluble HM1.24 protein result in DC cell stimulation of T cells, but the T cells strongly react with autologous tumor cells. *See* Applicants' specification, e.g., Figure 1, Example 1, and Table 1. Furthermore, Applicants discovered that in 5 MM patients, HM1.24-specific T cells respond to autologous plasma cells. *Id.* at Examples 1 and 2. These unexpected advantages would not have been anticipated by the combination of the cited references.

B. Chiriva-Internati from Final Office Action

Contrary to the present disclosure, Chiriva-Internati describes a viral vector comprising a HM1.24 ***gene***, and not pulsing a dendritic cell with a soluble ***protein/peptide***. Thus, Chiriva-Internati discloses that a strong CTL activity is caused by *expressing* full length HM1.24 in DC cells.

Also, it is not surprising that Chiriva-Internati discloses using a full length HM1.24 because using less than a full length HM1.24 sequence could fail to activate CTL, as a shortened sequence may not contain residues required for activating CTL. For example, HM1.24 residues necessary for activating CTL may be deleted in creating a soluble protein/peptide.

Additionally, while the Office understands that the rationale to modify or combine the prior art may be expressly or impliedly contained in the prior art or reasoned from knowledge available to a skilled artisan, the Office still disregards the MPEP and patent laws, and makes the rejection without consideration of the teachings in the art which discourage the combination. In fact, it appears that the Office is improperly using hindsight reconstruction to arrive at the presently claimed invention.

For example, Chiriva-Internati teaches that for introduction of a protein into dendritic cells, the protein must be continuously expressed by introducing HM1.24 gene-containing viral vector into dendritic cells because the half life of the protein is very short. Accordingly,

Chiriva-Internati, a reference heavily relied upon by the Office in the rejection, destroys the motivation for pulsing a soluble HM1.24 protein/peptide into dendritic cells.

Furthermore, the Office withdrew the previous obviousness rejection of the claims over Treon, in view of Ohtomo and Chiriva-Internati. Thus, the Office recognized the deficiencies in the teachings of these references. Although the current rejection supplements the primary references with WO 200177362 and Porgador, and optionally Thurner, the addition of a reference which relates to immunoassays (WO 200177362), dendritic cells pulsed with class I restricted peptides (Porgador), and/or dendritic cells pulsed with Mage-3A-1 (Thurner) do not cure these deficiencies either, especially when nothing in the cited art would not lead a skilled artisan to specifically use a soluble HM1.24 protein or peptide to make a cancer vaccine, or recognize the unexpected advantages in doing so.

Thus, the art does not provide the motivation to combine the references and teach each and every element of the presently claimed invention. Therefore, for at least the reasons provided herein, Applicants respectfully request the rejections be withdrawn.

CONCLUSION

Applicants believe that the present application is in condition for allowance and request favorable reconsideration.

The Examiner is invited to contact the undersigned if a telephone interview would advance prosecution.

Respectfully submitted,

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